Tumor Ecology and Complementary Information

BIRS Integrative Analysis of Emerging Biological Data Types
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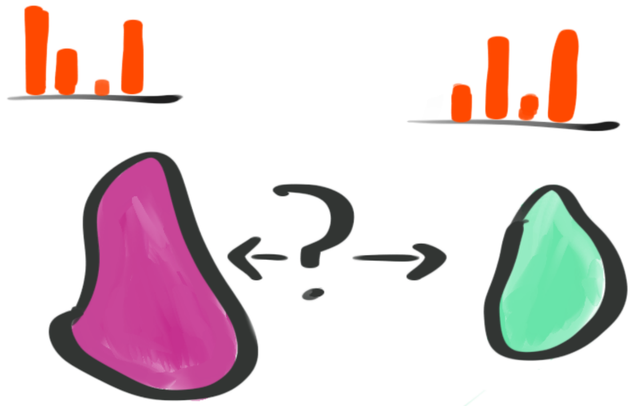
Code: github.com/krisrs1128/birs_mini
Vis: https://observablehq.com/@krisrs1128/spatial-vs-expression-map
Binder: https://mybinder.org/v2/gh/krisrs1128/birs_mini/master?urlpath=rstudio
Slides: https://tinyurl.com/yanphfmg

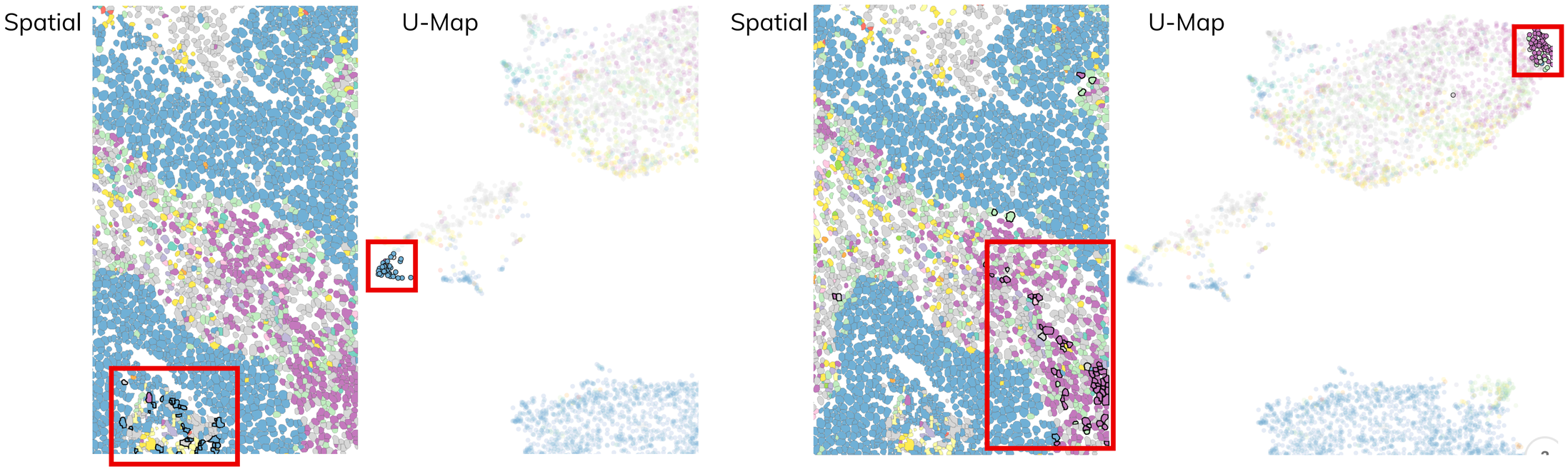
Problem Setting

- Tumor ecosystems
  - We can now study cancers as ecosystems of interacting cells
  - Interactions have consequences for disease progression
- Data sources
  - Mass Spectrometry: Composition of the cells in the ecosystem
  - MIBI-TOF: Interactions between cells



Interactive Visualization

- Linked Brushing: Combine (literal) spatial map with abstract (U-)map
- Within cell-types, some U-Map clusters are spatially co-located, but far from universal



Examples where U-Map clusters correspond to spatially nearby cells. Immune highlighted in left pair, tumor on right.

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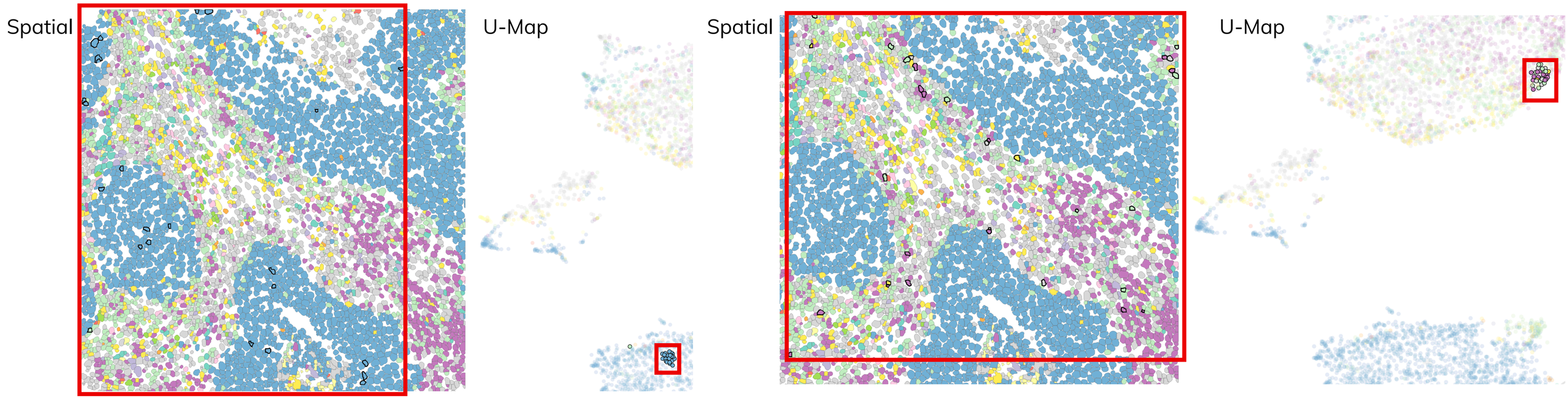
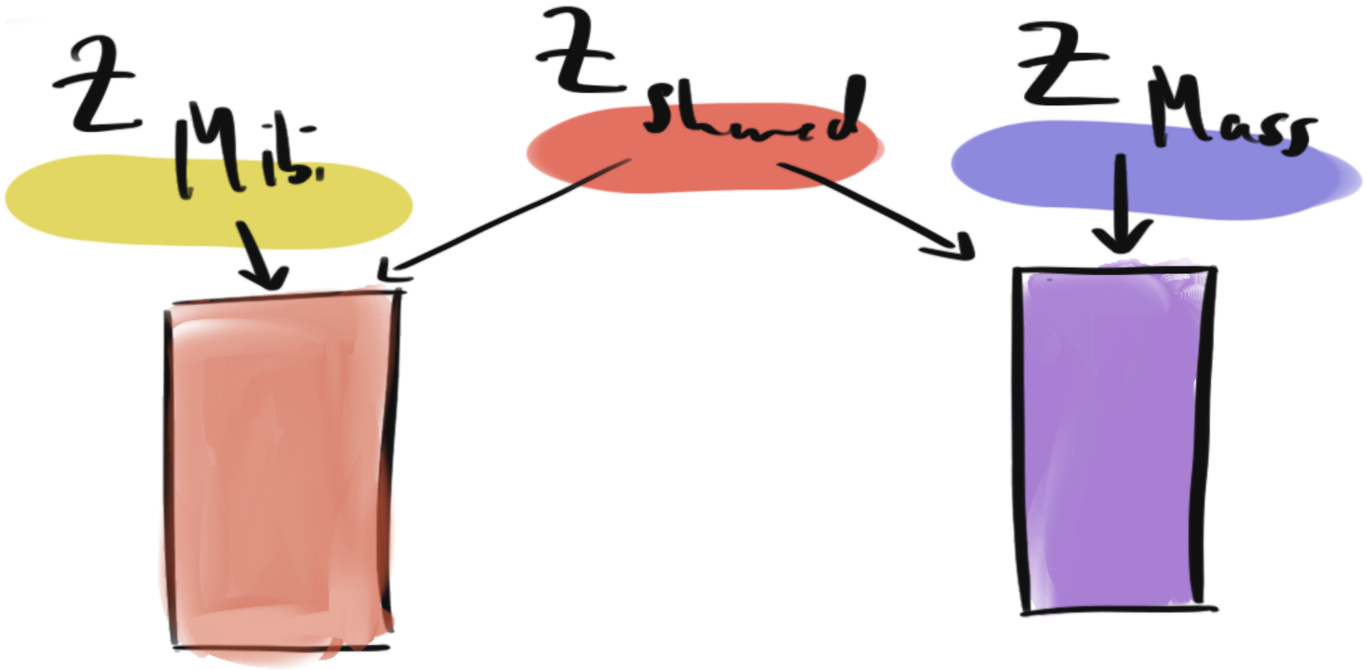


Examples where U-Map clusters are spatially diffuse. Immune cells highlighted in left pair, tumor on right.

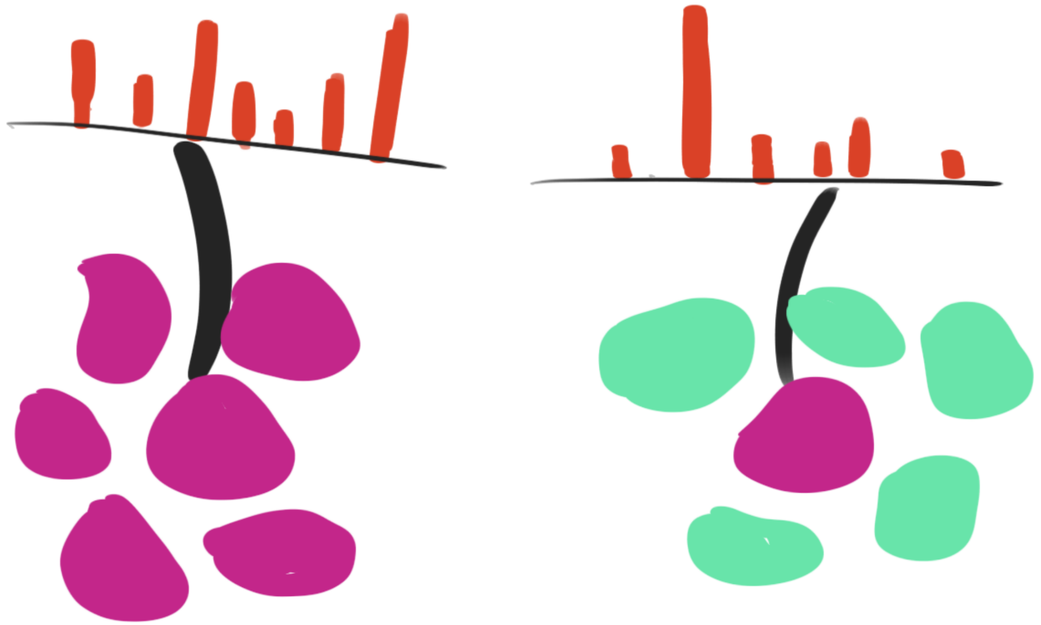
Cell-Level Analysis

- Can we recover shared latent phenomena?
- To what extent can a simple assay be a proxy for a powerful one?
  - Can the trade-offs guide experimental design?



Proposal: Direct inversion

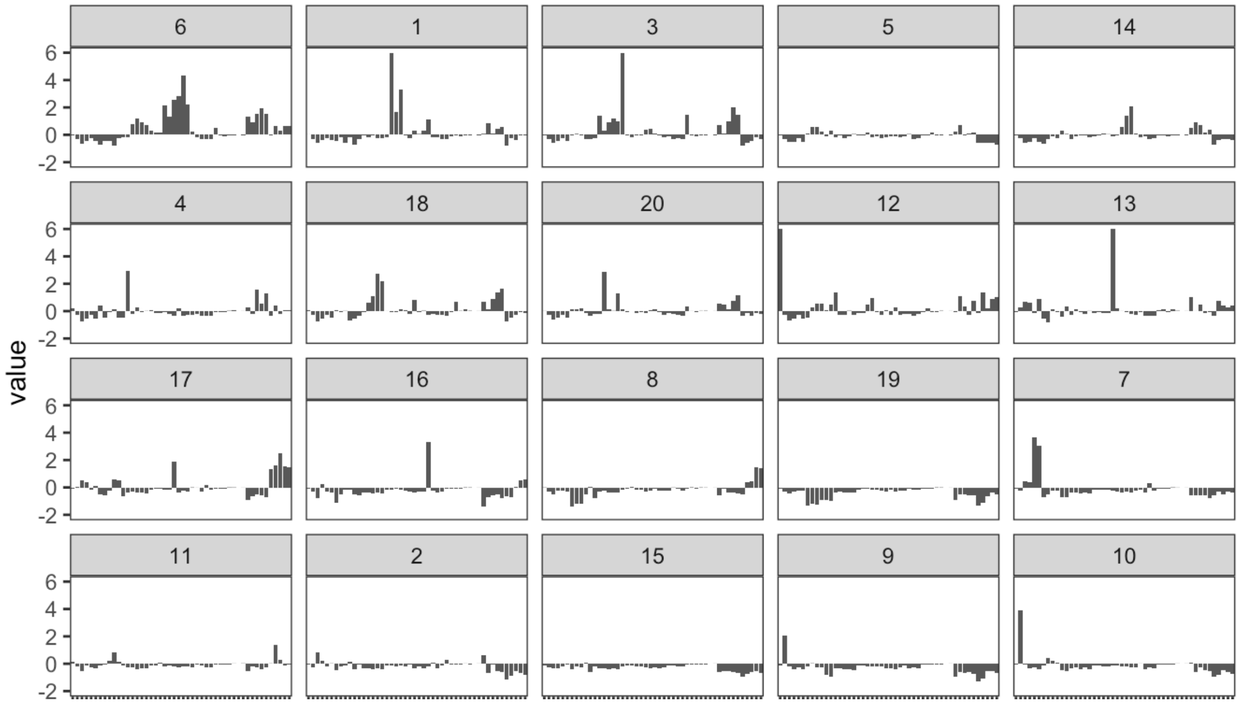
- Rigorous: latent variable analysis, specifying full generative mechanism
- Hack (but simple!): *Train* a protein-to-spatial expression model using MIBI-TOF, and then *test* that on Mass Spec
- Find whether given configurations of neighboring cells force specific expression patterns (especially if configuration is unrelated to simply composition)... by trying to learn the inverse



Proposal: Direct inversion

Recipe,

1. ***Cluster***: Make clusters, from expression data
2. ***Featurize***: Define spatial features
3. ***Embed***: Reduce dimensionally of spatial features
4. ***Predict***: Using expression alone, predict spatial embeddings
    A. Only use proteins available in Mass Spec



20 centroids from the clustering. Each column is a protein.

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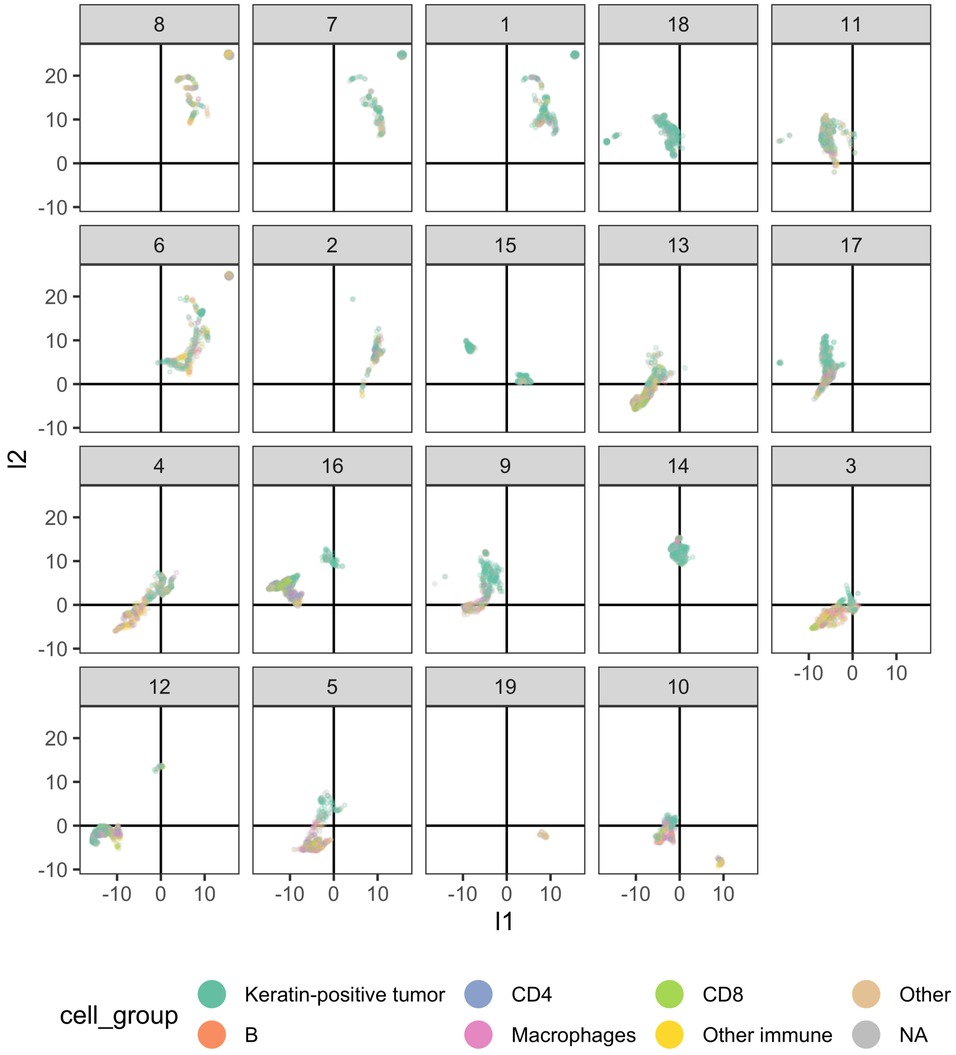

Embeddings of the neighborhood proportion vectors.

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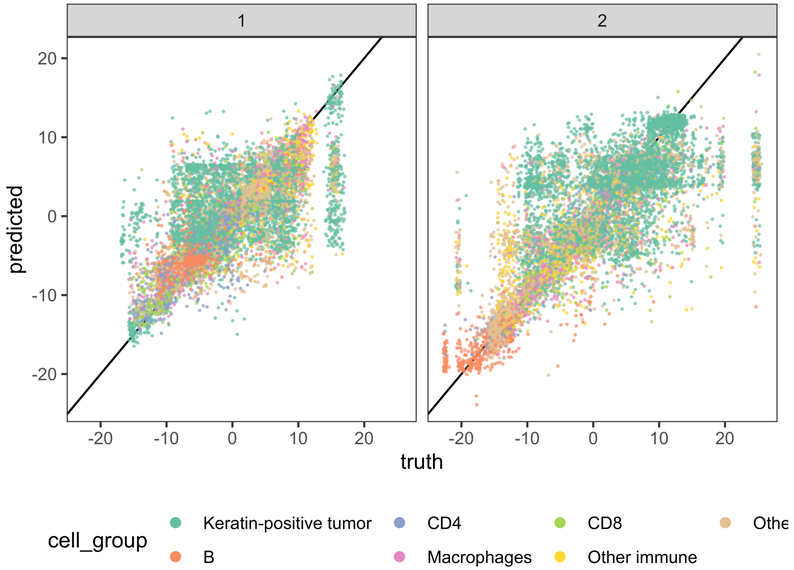
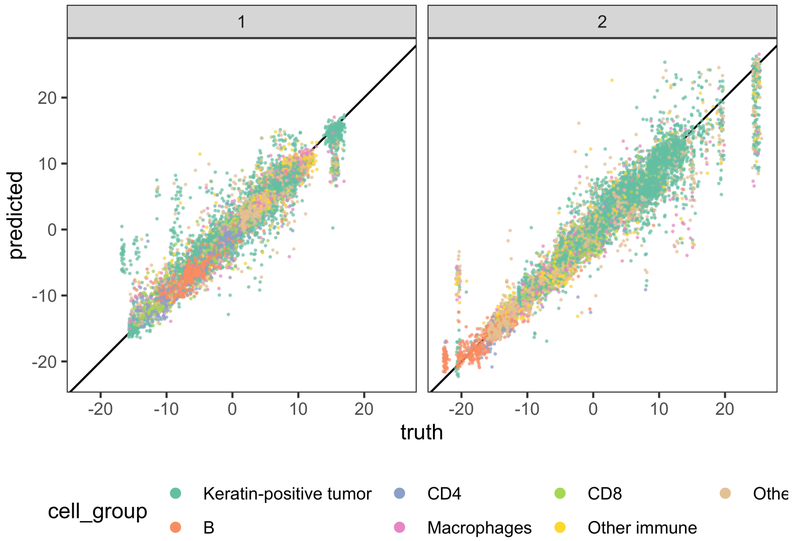
(a)



(b)



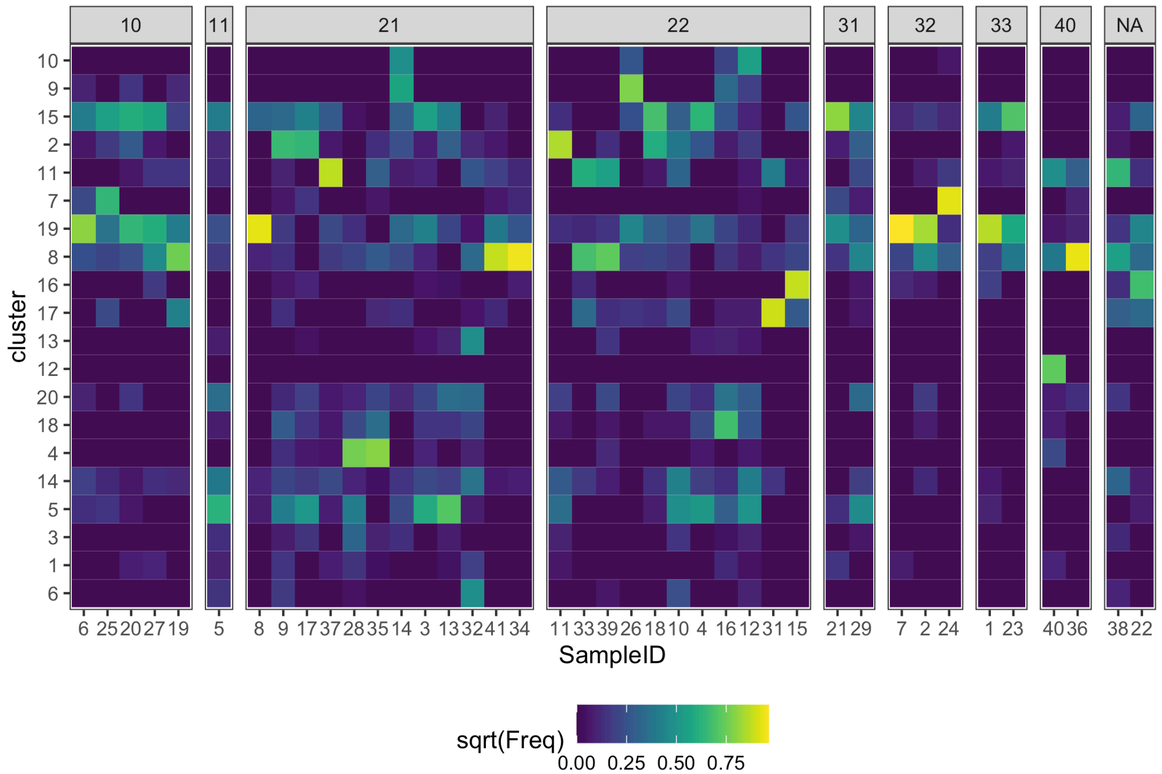
Prediction performance, when using expression data from (a) just mass spec and (b) using all proteins. Two columns are two dimensions of the embedding.

Sample-Level Analysis

- Many scientific claims are about the entire ecosystem, not individual cells
  - E.g., Tumor heterogeneity
- Interaction vs. Composition
  - Interactions between cells might be hard to find
  - Ecosystem properties may be visible from composition alone

Expression -> Spatial (Sample Level)

- Recipe,
    1. ***Cluster***: Make clusters, from expression data
    2. ***Featurize***: Define spatial features
    3. ***Aggregate***: Data are at cell level, but we need summaries at sample level. So compute functions of spatial features / find cluster mixing %s.
    4. ***Predict***: Predict spatial features from cluster counts in (2)
- Intuition: I(X, Y) is large if communication channel has low noise



The representation of each sample (column), based on the %s of cells it has from different clusters.

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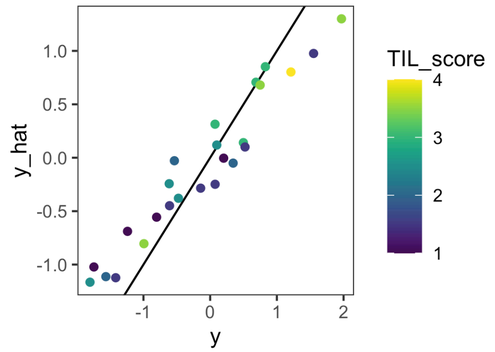

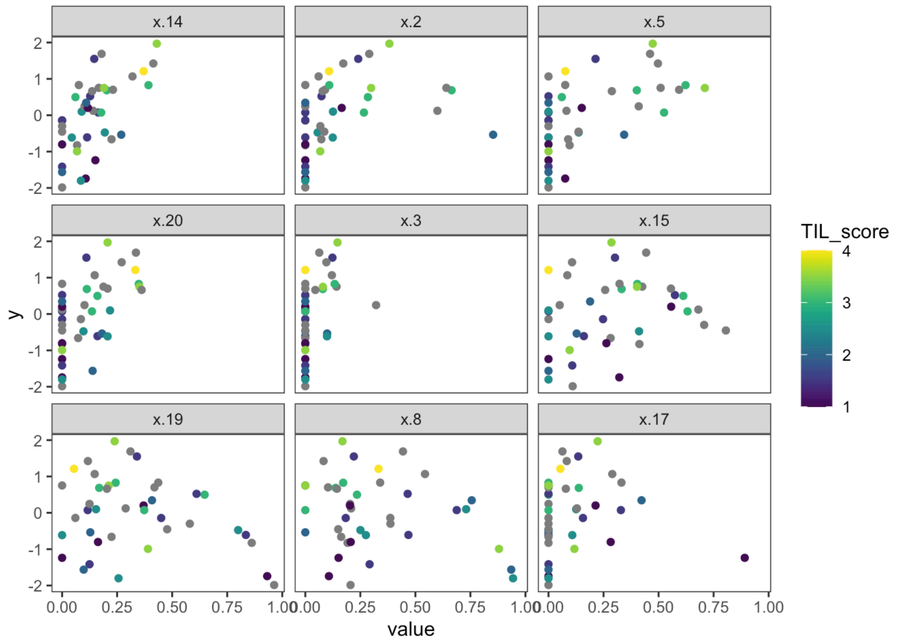

Predicting the average cluster entropy of all the 5-nearest neighbor balls within a person, based only on expression data.

Phenotype = Spatial + Composition

- As an alternative measure of redundancy, see how much performance improves when combining two tables
  - In linear regression, adding redundant variable decreases performance
- Approach only works if we have easily predictable phenotypic characteristics

Spatial

mtry	RMSE	Rsquared	MAE
2	0.9747601	0.1128382	0.8176102
3	0.9978172	0.1054846	0.8295354
4	1.0084429	0.1107027	0.8332106

Expression

mtry	RMSE	Rsquared	MAE
2	0.8173901	0.3116003	0.7030003
11	0.8713073	0.1950925	0.7456817
20	0.9029941	0.1718520	0.7682995

Combined

mtry	RMSE	Rsquared	MAE
2	0.7697287	0.3943017	0.6667050
13	0.8187737	0.2448980	0.7056521
24	0.8478903	0.2337036	0.7246190

Ability to predict TIL increases when we include both sets of features, but there is overlap. Caveat: there are only 25 samples with TIL score available.

Takeaways + Next Steps

- The rows and columns of X should not be taken for granted
  - Several definitions of sampling units work (i.i.d. is a construct)
  - The features must be defined (really, should be learned)
- Degree of redundancy, and source-specific signal, are important
  - It would have been if weird spatial patterns were exactly recoverable from Mass Spec
  - Potentially useful meta-tool (wrapping integrative ‘omic algorithms)